Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

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Abstract

Following the adoption of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods, the European Commission requested EFSA to update and develop scientific and technical guidance for the preparation and presentation of applications for authorisation of novel foods. This guidance presents a common format for the organisation of the information to be presented in order to assist the applicant in preparing a well-structured application to demonstrate the safety of the novel food. The application should be comprehensive and complete. This guidance outlined the data needed for the safety assessments of novel foods. Requirements which should be covered in all applications relate to the description of the novel food, production process, compositional data, specification, proposed uses and use levels, and anticipated intake of the novel food. Further sections on the history of use of the novel food and/or its source, absorption, distribution, metabolism, excretion, nutritional information, toxicological information and allergenicity should be considered by the applicant by default. If not covered in the application, this should be justified. The applicant should integrate the data presented in the different sections to provide their overall considerations on how the information supports the safety of the novel food under the proposed conditions of use. Where potential health hazards have been identified, they should be discussed in relation to the anticipated intakes of the novel food and the proposed target populations. On the basis of the information provided, EFSA will assess the safety of the novel food under the proposed conditions of use.

Keywords: guidance, novel foods, traditional foods, authorisation, safety, toxicity

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Summary

Following the adoption of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods, the European Commission requested the European Food Safety Authority (EFSA) to update and develop scientific and technical guidance for the preparation and presentation of applications for authorisation of novel foods.

This guidance presents a common format for the organisation of the information to be presented in order to assist the applicant in the preparation of a well-structured application to demonstrate the safety of the novel food. Adherence to this format will facilitate easy access to information and scientific data in applications to help EFSA to carry out its evaluation and to deliver its scientific opinion in an effective and consistent way. This guidance is also intended to provide the type and quality of information EFSA needs to conclude whether or not the novel food is safe under the proposed conditions of use.

This guidance outlines the data needed to carry out the safety assessments of novel foods. Requirements which should be covered in all applications relate to the description of the novel food, production process, compositional data, specification, proposed uses and use levels, and anticipated intake of the novel food. Further sections on the history of use of the novel food and/or its source, absorption, distribution, metabolism, excretion, nutritional information, toxicological information and allergenicity should be considered by the applicant by default. If not covered in the application, this should be justified. Duplication of animal testing should be avoided, where possible.

The applicant should integrate the data presented in the different sections to provide their overall considerations on how the information supports the safety of the novel food under the proposed conditions of use.

Where potential health hazards have been identified (e.g. on the basis of the composition of the novel food, its production process, its history of use, results from animal or human studies), they should be discussed in relation to the anticipated intakes of the novel food and the proposed target populations.

On the basis of the information provided, EFSA will assess the safety of the novel food under the proposed conditions of use.

The guidance document was subject to public consultation (from 18 February to 21 April 2016) and a stakeholder meeting (11 April 2016) before finalisation.

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Background as provided by the European Commission

On 25 November 2015, the European Parliament and the Council adopted the Regulation of the European Parliament and of the Council on novel foods.[1]

The Regulation requires that all applications for the authorisation of novel foods shall be submitted to the Commission who may then request a risk assessment from the European Food Safety Authority (EFSA). In assessing the safety of novel foods, EFSA shall, where appropriate, consider the following:

1) whether the novel food concerned is as safe as food from a comparable food category already existing on the market within the Union;
2) whether the composition of the novel food and the conditions of its use do not pose a safety risk to human health in the Union;
3) a novel food, which is intended to replace another food, does not differ from that food in such a way that its normal consumption would be nutritionally disadvantageous for the consumer.

The Regulation also introduces a special procedure for safety assessment for traditional foods from third countries, based on a history of safe food use. In this case, a notification for the placing on the market of a traditional food from a third country is sent to the Commission who forwards it to all the Member States and EFSA. A Member State or EFSA may submit duly reasoned safety objections on the placing on the market of the notified food. In this latter case, the applicant may transform the notification into an application, for which a safety evaluation will be requested from EFSA. In assessing the safety of these types of novel foods, EFSA shall, where appropriate, consider the following:

1) whether the history of safe food use in a third country is substantiated by reliable data submitted by the applicant;
2) whether the composition of the food and the conditions of its use do not pose a safety risk to human health in the Union;
3) where the traditional food from the third country is intended to replace another food, whether it does not differ from that food in such a way that its normal consumption would be nutritionally disadvantageous for the consumer.

The Commission shall adopt implementing rules on administrative and scientific requirements for the preparation and the presentation of the applications for novel foods, as well as for the notifications and applications for traditional foods from third countries for the scientific assessment, respectively, in accordance with Article 13 and Article 20 of the Regulation. These implementing measures need to be complemented with scientific and technical guidance regarding the information that needs to be submitted by the applicants. In this context, the current Commission Recommendation 97/618/EC,[2] which is in place for the additional safety assessment of the novel food applications under the current rules (Regulation (EC) No 258/97[3]), should serve as the basis for updating the guidance on preparation and presentation of applications for novel foods.

Terms of Reference as provided by the European Commission

In accordance with Article 29 of Regulation (EC) No 178/2002, the European Commission asks EFSA to update and develop scientific and technical guidance for the preparation and presentation of applications for authorisation of novel foods, and to develop scientific and technical guidance for notifications and applications for authorisation of Traditional Foods from third countries.

Objectives

This guidance presents a common format for the organisation of the information to be presented in order to assist the applicant in the preparation of a well-structured application to demonstrate the safety of the novel food. Adherence to this format will facilitate easy access to information and scientific data in applications to help EFSA to carry out its evaluation and to deliver its scientific opinion in an effective and consistent way.

[1] Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (2013/0435 (COD). OJ L 327, 11.12.2015, p. 1–22.
[2] OJ L 253, 16.9.1997, p. 1.
[3] OJ L 43, 14.2.1997, p. 1.

This guidance is also intended to provide the type and quality of information EFSA needs to conclude whether or not the novel food is safe under the proposed conditions of use. The requirements for preparing and presenting a dossier for the notification of a traditional food from a third country are dealt with by a separate guidance document EFSA NDA Panel (2016a).

It is intended that the guidance will be kept under review and it will be further updated as appropriate in the light of experience gained from the evaluation of novel food applications.

Scope

The guidance presented in this document is for preparing and presenting applications for authorisation of a novel food under Article 10 of Regulation (EU) 2015/2283.

A separate EFSA guidance document is available to assist applicants in preparing and presenting a notification dossier for a traditional food from a third country under Article 14 of Regulation (EU) 2015/2283 (EFSA NDA Panel, 2016a). The latter document specifically addresses the data required to substantiate the 'history of safe food use in third country' of a traditional food, as defined by Article 3 of Regulation (EU) 2015/2283. Under the notification procedure, Regulation (EU) 2015/2283 foresees that a Member State or EFSA may submit to the Commission duly reasoned safety objections to the placing on the market within the Union of the traditional food concerned. In such cases, the present guidance should also serve applicants in preparing and presenting an application under Article 16 of Regulation (EU) 2015/2283, where the application concerns data other than those on the 'history of safe food use in a third country'.

Definitions

As per Article 3, paragraph 2 of Regulation (EU) 2015/2283, the following definition applies:

(a) '*Novel food*' means any food that was not used for human consumption to a significant degree within the Union before 15 May 1997 irrespective of the dates of accession of Member States to the Union and that falls under at least one of the following categories:

i) food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997;
ii) food consisting of, isolated from or produced from microorganisms, fungi or algae;
iii) food consisting of, isolated from or produced from material of mineral origin;
iv) food consisting of, isolated from or produced from plants or their parts, except when the food has a history of safe food use within the Union and is consisting of, isolated from or produced from a plant or a variety of the same species obtained by:
   - traditional propagating practices which have been used for food production within the Union before 15 May 1997; or
   - non-traditional propagating practices which have not been used for food production within the Union before 15 May 1997, where those practices do not give rise to significant changes in the composition or structure of the food affecting its nutritional value, metabolism or level of undesirable substances;
v) food consisting of, isolated from or produced from animals or their parts, except for animals obtained by traditional breeding practices which have been used for food production within the Union before 15 May 1997 and the food from those animals has a history of safe food use within the Union;
vi) food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, microorganisms, fungi or algae;
vii) food resulting from a production process not used for food production within the Union before 15 May 1997, which gives rise to significant changes in the composition or structure of a food, affecting its nutritional value, metabolism or level of undesirable substances;
viii) food consisting of engineered nanomaterials as defined in point (f) of Article 3, paragraph 2 of Regulation (EU) 2015/2283;
ix) vitamins, minerals and other substances used in accordance with Directive 2002/46/EC, Regulation (EC) No 1925/2006 or Regulation (EU) No 609/2013, where:

- a production process not used for food production within the Union before 15 May 1997 has been applied as referred to in point (a) (vii) of this paragraph; or
- they contain or consist of engineered nanomaterials;

x) food used exclusively in food supplements within the Union before 15 May 1997, where it is intended to be used in foods other than food supplements as defined in point (a) of Article 2 of Directive 2002/46/EC.

General principles

1) This document should be read in conjunction with Regulation (EU) 2015/2283 of the European Parliament and of the Council as regards novel foods and the current and future European Union (EU) guidelines and provisions. In addition, several guidance documents from EFSA are of relevance for the preparation of novel food applications. They are listed throughout the present document. Over time, new guidance documents will be developed which may be of relevance for novel food applications. Other EFSA guidance documents, for example, those from the EFSA Scientific Committee or the Panel on Food Additives and Nutrient Sources Added to Food might be applicable in specific cases. Applicants are therefore advised to consult the EFSA webpage and consider the most up-to-date versions of the available and applicable guidance documents.
2) The term 'application' hereafter means a stand-alone dossier containing the information and the scientific data submitted for the safety assessment of a novel food.
3) It is the duty of the applicant to provide all of the available (proprietary, confidential and published) scientific data (including both data in favour and not in favour) that are pertinent to the safety of the novel food. As such, an application to demonstrate the safety of the novel food should be comprehensive and complete.
4) The identification of data pertinent to the safety of the novel food should be performed and documented in order to demonstrate that the application covers the complete information available on the novel food. Information on the search strategy, including the sources used to retrieve pertinent data (databases, other sources), the terms and limits used (e.g. publication dates, publication types, languages, population, default tags) should be provided. Where applicable, the published literature should be reviewed by taking into account systematic review principles (EFSA, 2010). Full study reports should be provided if available.
5) This guidance presents a common format for the organisation of the information in order to assist applicants in the preparation of well-structured applications. Adherence to this format will facilitate easy access to information and scientific data in applications to help the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) to carry out its evaluation and to deliver its scientific opinion in an effective and consistent way.
6) The structure of the application should follow the sections presented in this guidance. The information required on the identity of the novel food (Section 2.2), production process (Section 2.3), compositional data (Section 2.4), specifications (Section 2.5), and proposed uses and use levels and anticipated intake of the novel food (Section 2.7) constitute the minimum requirements which must be fulfilled in all applications. Further sections on the history of use of the novel food and/or of its source (Section 2.6), absorption, distribution, metabolism and excretion (Section 2.8), nutritional information (Section 2.9), toxicological information (Section 2.10) and allergenicity (Section 2.11) should be considered by the applicant. If not covered in the application, this should be justified.
7) The applicant should provide their considerations at the end of individual sections on how the information supports the safety of the novel food under the proposed conditions of use. Uncertainties should be addressed, and a critical appraisal on data both in favour and not in favour, of the safety of the novel food should be provided.
8) Analyses/tests should be performed in a competent facility that can certify the data. Quality systems in place for control/documentation should be indicated. Information on the accreditation of involved facilities and certificates of analyses should be provided. Whenever official guidelines (e.g. OECD, EMA and ICH) and quality systems (e.g. GLP, GMP, GCP and applicable ISO systems) were followed, the applicant should indicate compliance.
9) Deviations from the requirements specified in the respective sections described in this guidance should be justified.
10) The decision on confidential treatment of information submitted under Article 23 of Regulation (EU) 2015/2283 falls under the responsibility of the European Commission. As per Article 23(5)

of the Regulation, EFSA shall take necessary measures to ensure appropriate confidentiality of the information received under this Regulation, except for information which is required to be made public in order to protect human health.

11) The decision on granting the protection of proprietary data under Article 26 of Regulation (EU) 2015/2283 falls under the responsibility of the European Commission. With respect to the handling and use of proprietary data by EFSA, it should be noted that where evidence for the safety of a novel food includes a request for the protection of proprietary data, the NDA Panel considers in its opinion whether the safety of the novel food could have been assessed without the data claimed as proprietary by the applicant or not.

12) In accordance with Directive 2010/63/EU[4] on the protection of animals used for experimental and other scientific purposes, and as reiterated in Regulation (EU) 2015/2283, tests on animals should be replaced, reduced or refined. Duplication of animal testing should be avoided, where possible.

Organisation and content of the application

The following information should be provided in the application and the structure should follow a common format. Data provided in the application should be organised into three parts:

- Part 1 contains the administrative data, such as information relating to the applicant.
- Part 2 contains information specific to the novel food with respect to identity of the novel food (Section 2.2), production process (Section 2.3), compositional data (Section 2.4), specifications (Section 2.5), the history of use of the novel food and/or of its source (Section 2.6), proposed uses and use levels and anticipated intake (Section 2.7), absorption, distribution, metabolism and excretion (Section 2.8), nutritional information (Section 2.9), toxicological information (Section 2.10) and allergenicity (Section 2.11). It should include a list of all references.
- Part 3 comprises the glossary or abbreviations of terms quoted throughout the dossier, the certificates (on the accreditation of laboratories, certificates of analyses) and contains full copies/reprints of all pertinent scientific data (published and unpublished), full study reports, and scientific opinions of national/international regulatory bodies.

1. Part 1: Administrative data

1.1. Comprehensive table of contents of the dossier

1.2. Applicant

1.2.1. Company/organisation

Provide the name and address of the company or organisation.[5]

1.2.2. Contact person

Indicate the contact person authorised to communicate with EFSA on behalf of the applicant.[6]

1.3. Regulatory status outside the European Union

If the novel food has been submitted by the applicant to a regulatory body for authorisation outside the EU, please indicate the status of the evaluation by each regulatory body (if more than one), as appropriate:

☐ Under consideration

Specify the proposed conditions of use (if they are different), the date of submission, and the recipient regulatory body.

[4] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, OJ L 276, 20.10.2010, p. 33.

[5] In case more than one company or organisation submits a dossier, provide their names and addresses. Only one contact person should be authorised to communicate with EFSA.

[6] To facilitate communication, only one contact person should be indicated per dossier.

☐ Withdrawn

Specify the conditions of use (if they are different) of the novel food which was withdrawn, the date of withdrawal, the reasons for withdrawal. Indicate the regulatory body at the time of withdrawal.

☐ Authorised

Specify the conditions of use (if they are different) of the novel food which has been approved, the date of approval. Indicate the authorising regulatory body, and if available, provide a copy of the scientific opinion of the regulatory body which authorised the novel food (in Part 3).

☐ Rejected

Specify the date and the reasons of rejection. Indicate the regulatory body which rejected the novel food, and if available, provide a copy of the scientific opinion of the regulatory body which rejected the novel food (in Part 3).

2. Part 2: Characterisation of the novel food, technical and scientific data

2.1. Introduction

The novel food should be briefly described in an introductory paragraph, including the source, the principle of the production process and typical compositional features. Its purpose and intended use should be described.

2.2. Identity of the novel food

Information on the identity of the novel food should be provided, depending on the class(es) under which the novel food falls. The Panel notes that the proposed classification is based on the chemistry, production process and source of novel foods, for the purpose of the scientific assessment, and is not meant to reflect the regulatory categories outlined in Article 3(2)a of the Regulation. There may be cases where a novel food could be allocated to two or more classes (e.g. 'chemical substances' and 'food produced by a microorganism'). In such cases, the relevant information for all applicable classes should be provided.

2.2.1. Chemical substances

- Chemical name, when appropriate, according to IUPAC nomenclature rules
- CAS number (if this has been attributed) and other identification numbers
- Synonyms, trade names, abbreviations
- Molecular and structural formulae; stereochemistry
- Molecular mass (Da)

2.2.2. Polymers

- Structural formulae of monomers and starting materials, reagents involved in the polymerisation
- Structure of the polymer, number average molecular weight and weight average molecular weight
- Nature and degree of modification of the polymer
- Particle size, shape and distribution

2.2.3. Foods consisting of, isolated from or produced from microorganisms, fungi or algae

- Scientific (Latin) name (family, genus, species, strain) according to the international codes of nomenclature
- Synonyms that may be used interchangeably with the preferred scientific name
- For algae[7] and fungi,[8] verification of the identity according to internationally recognised databases and methodology

[7] For algae species: The Algae database (www.algaebase.org)
[8] For the identification of fungi: The *Index fungorum*: http://www.indexfungorum.org/names/names.asp for identification of fungi.

- For bacteria and yeasts (unicellular organisms), verification of the species and strain identity according to internationally accepted methods; information on applicable methods for the characterisation of bacteria and yeasts are provided in the EFSA Health Claim guidance (EFSA NDA Panel, 2016b). Molecular methods allow predictions of genes encoding for toxins, antimicrobial resistance and other pathogenic factors
- Origin of the organism
- If available, deposition in an officially recognised culture collection with access number

2.2.4. Food consisting of, isolated from or produced from material of mineral origin

This section concerns inorganic mineral constituents isolated from rocks and utilised as inorganic or organic salts or chelates.

- Chemical name according to IUPAC nomenclature rules
- CAS number (if this has been attributed) and other identification numbers
- Synonyms, trade names, abbreviations
- Molecular and structural formulae
- Molecular mass (Da)
- Particle size, shape, crystal form, distribution

2.2.5. Food consisting of, isolated from or produced from plants or their parts[9]

- Scientific (Latin) name (botanical family, genus, species, subspecies, variety with author's name, chemotype, if applicable) according to the international codes of nomenclature
- Synonyms (botanical name) that may be used interchangeably with the preferred scientific name
- For plants[10] verification of the identity according to internationally recognised databases and methodology
- Common names (if a trivial or a common name is used, it should be linked to the scientific name and part used)
- Part(s) used (e.g. root, leaf, seed, etc.)
- Geographical origin (continent, country, region)

2.2.6. Food consisting of, isolated from or produced from animals or their parts

- Scientific (Latin) name (zoological family, genus, species, subspecies, breed, if applicable)
- Synonyms that may be used interchangeably with the preferred scientific name
- Common names (if a trivial or a common name is used, it should be linked to the scientific name and part used)
- Part(s) used
- Geographical origin (continent, country, region)

2.2.7. Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, fungi or algae

This section concerns cultures derived from multicellular origin (animals, plants including algae and mushrooms). Foods originating from cultures of unicellular origin should be addressed under 2.2.3.

- Biological source (taxonomic information on family, genus, species, subspecies, variety) according to the international codes of nomenclature
- For plants,[10] algae[7] and fungi,[8] verification of the identity according to internationally recognised databases and methodology
- Organ and tissue or part of the organism sourced
- Laboratory or culture collection sourced

[9] These requirements are in line with the EFSA Scientific Committee guidance on the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA Scientific Committee, 2009a).

[10] The Plant List (www.theplantlist.org) resulting from the Collaboration between the Royal Botanic Gardens, Kew and Missouri Botanical Garden; The USDA-ARS Germplasm Resources Information Network (GRIN) database (https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx) in case The Plant List does not provide the required information; The International Plant Names Index (http://www.ipni.org/) in case the two above sources do not provide the required information.

- Information on the identity of cells
- Cell or tissue substrate used as a novel food
- Type of cultures

2.2.8. Foods consisting of 'engineered nanomaterials'[11]

For novel foods containing or consisting of 'engineered nanomaterials', the parameters for characterisation and identification of engineered nanomaterials are outlined in the EFSA Scientific Committee guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain (EFSA Scientific Committee, 2011a). The Panel notes that the guidance is currently being updated by EFSA (EFSA-Q-2016-00281[12]).

2.3. Production process

2.3.1. Detailed description of the production process

The process(es) employed to produce the novel food (e.g. chemical synthesis, enzyme-catalysis, fermentation or isolation from a natural source, etc.) should be described. The description of the production process should be detailed enough to provide the information that will form the basis for the evaluation of the bioavailability, nutritional value and safety, which should be addressed in the respective sections. With regard to safety, the description should include information on potential by-products, impurities or contaminants.

The applicant should inform whether a production process is novel, i.e. not used for food production within the Union before 15 May 1997, and characterise the novel aspects of the process.

Information should also be provided on the handling of the sources, for example, the propagation, growth and harvesting conditions for plants and fungi (e.g. wild or cultivated, cultivation practices, time of harvest in relation to both season and stage of the plant growth); the breeding, rearing, feeding and farming conditions for farmed animals or the hunting, catching or collecting and killing of wild living animals; the culture conditions for microorganisms and algae, and cell culture or tissue culture from plants and animals. The description of the cultivation of plants, fungi, algae and microorganisms and the rearing of animals should also include information on the use of pesticides, antimicrobials and antiparasitic agents.

Post-harvest handling, e.g. transport, drying techniques and storage conditions (duration, light, moisture and temperature) of unprocessed foods and the raw materials for further processing should be described. The parts of the organism used as a raw material should be specified and information on other starting substances or materials should be provided.

For novel foods consisting of, isolated from or produced from plant, animal or microbiological sources, the applicant should describe in detail the process by which the raw material is converted into an ingredient or a preparation intended for a food product. Examples may include heat treatment, extraction, distillation, squeezing, fractionation, purification, concentration, fermentation, or other procedure(s). Information on substances used in the manufacturing process, e.g. identity of the extraction solvents, ratio of extraction solvent to the material, reagents, residues remaining in the final product and any special precautions (light and temperature) should be provided.

For novel foods obtained via chemical synthesis, the reaction sequence, side reactions and purification steps should be described. Information on reaction conditions (e.g. reagents, temperature, duration of the reaction, and catalyst), chemical or physical purification methods (e.g. solvent extraction and crystallisation) should be reported.

Operational limits and key parameters of the production process should be given. Measures implemented for production control and quality and safety assurance should be described (e.g. HACCP, GMP, ISO). A production flow chart should be provided, including quality and safety control checks. Standardisation criteria (e.g. chemical markers for the novel food) should be provided.

For novel foods consisting of, isolated from or produced from plants-specific considerations and complementary information are provided in the EFSA guidance on safety assessment of botanicals and botanical preparations (EFSA Scientific Committee, 2009a).

[11] As defined in Regulation (EU) 2015/2283.
[12] http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2016-00281

2.3.2. Non-confidential description of the production process

If the detailed description on the production process (Section 2.3.1) contains confidential elements, the applicant is asked to provide a non-confidential summary of the production process of between half to a maximum of a page in length.

2.4. Compositional data

The information should include qualitative and quantitative data on the composition as well as physicochemical, biochemical properties and microbiological characterisation of the novel food.

Section 2.4.1 outlines general data requirements applicable to all novel foods. Sections 2.4.2 and 2.4.3 set specific requirements depending on whether the novel food is a single substance or a simple mixture thereof, a complex mixture or a whole food.[13]

Validated methods should be used for the analyses, preferably nationally or internationally recognised methods (e.g. Association Of Analytical Communities, American Chemical Society, European Pharmacopoeia). The respective methods of analysis should be described together with their references. The information on analyses for substances of toxicological concern should also include their limit of detection and limits of quantification. Certificates of analyses and information on the accreditation of laboratories should be provided. If in-house methods are employed, they should be fully described, and the results of the respective validation procedures should be provided. If the analyses are not performed in accredited laboratories, justification should be provided. Analytical data from publications can also be used if the publications provide sufficient information on the laboratory where analyses have been carried out, the methods utilised, and if the studies were performed on representative samples of the novel food. Available published data can also contribute to provide information on the variability of the composition of the novel food.

Compositional data and their variability should support the setting of specifications of the novel food how it is intended to be placed on the market (Section 2.5). The analytical information should be provided preferably on at least five representative batches of the novel food that have been independently produced (i.e. with independent batches of raw materials). When several production processes are proposed, such data should be provided for each process.

2.4.1. General requirements

Information on the identities and the quantities of impurities or by-products, residues and chemical and microbiological contaminants should be provided (e.g. heavy metals, mycotoxins, PCBs/dioxins, pesticides). The type and spectrum of potential target analytes should be considered in the light of the sources and the production process. For example, for substances obtained by chemical synthesis, residual starting materials and by-products anticipated from side-reactions should be analysed; for substances produced by microbial fermentation, the presence of undesirable metabolites should be investigated; for substances isolated by extraction, data on residues of the solvent used should be provided.

2.4.2. Single substances and simple mixtures thereof

Simple mixtures are mixtures whose components can be fully chemically characterised. For simple mixtures of defined substances, information on the identities and the relative ratios of all components should be provided. This should allow the elaboration of a mass balance.

For single substances, the following data should be provided:

- Identity tests (e.g. UV-VIS, IR, NMR, GC–MS, LC–MS)
- Physicochemical properties (e.g. appearance, melting point, boiling point)
- Solubility data in water and other common solvents
- Particle size, shape and distribution
- Minimum purity value
- Density and/or viscosity for liquid preparations

For single substances and their mixtures produced with genetically modified microorganisms (GMMs), applicants are referred to the requirements for GMMs Category 1 (i.e. chemically defined purified compounds and their mixtures in which both GMMs and newly introduced genes have been

[13] As defined by the Scientific Committee (EFSA Scientific Committee, 2011a), https://www.efsa.europa.eu/en/efsajournal/pub/2438

removed, e.g. amino acids, vitamins) as laid down by the EFSA guidance on the risk assessment of GMMs and their products intended for food and feed use (EFSA GMO Panel, 2011).

2.4.3. Complex mixtures and whole foods

Complex mixtures (e.g. extracts, protein hydrolysates) and whole foods (e.g. milk, meat, fruits, seeds) are defined as those where all constituents cannot be fully chemically characterised and/or identified.

A qualitative and quantitative characterisation of the main constituents should be performed, at least via sum parameters. For whole foods, this should include proximate analyses (i.e. ash, moisture, protein, fat, carbohydrates). On the basis of these data, a mass balance should be calculated. The amount of unidentified components should be indicated and should be as low as possible.

For the classes of naturally or chemically derived components which characterise the nature of the novel food (e.g. peptides, phospholipids, carotenoids, phenolics, sterols), comprehensive qualitative and quantitative data should be provided.

Qualitative and quantitative data on nutritionally relevant inherent constituents (e.g. micronutrients) should be given.

Taking into account the source of the novel food, qualitative and quantitative data on inherent substances of possible concern to human health (e.g. toxic, addictive, psychotropic, allergenic) should be provided).

In addition to analytical data on composition analysis data, a literature search should be performed according to the methodology developed by EFSA (2010) to retrieve published compositional data for the source and the part used in/as novel food. Information on the used keywords and applied inclusion/exclusion criteria for the literature search should be provided.

Any substances of concern derived from plants should be classified according to their chemical structure. Levels at which the constituents are present in the respective part of the botanical or botanical preparation should be given where available. It is recommended that chemical fingerprinting of the botanical material is undertaken for this purpose.

Particular attention should be given to the possible presence of genotoxic and/or carcinogenic substances.

The following non-exhaustive tools can help identifying the possible substances of concern in a botanical material:

- The EFSA Compendium of Botanicals, which provides information on naturally occurring substances that may be of concern for human health (EFSA Scientific Committee, 2012a),[14]
- The EFSA Chemical Hazard Database (S-IN, 2015).

For complex mixtures produced with genetically modified microorganisms (GMMs), applicants are referred to the requirements for GMMs Category 2 (i.e. complex products in which both GMMs and newly introduced genes are no longer present, e.g. cell extracts, most enzyme preparations) as laid down by the EFSA guidance on the risk assessment of GMMs and their products intended for food and feed use (EFSA GMO Panel, 2011).

2.4.4. Stability

The stability of the novel food should be evaluated in order to identify hazards which might arise during storage and transport. The nature of degradation products should be characterised.

Stability tests should consider constituents and parameters of the novel food which may be susceptible to changes during storage and which may affect its safety or serve as indicators for alterations which could have an impact on the safety of the novel food.

Depending on the nature and type of the novel food, the testing should address the physicochemical, biochemical and microbiological stability of the novel food under normal conditions of storage including the effects of packaging, the storage temperature and the environment (light, oxygen, moisture, relative humidity). Information on the normal storage conditions of the novel food should be provided as well as on the storage conditions under which the stability testing was performed. The stability testing should be provided on preferably at least five representative batches of the novel food that have been independently produced (i.e. with independent batches of raw materials).

[14] https://www.efsa.europa.eu/en/data/compendium-botanicals

The duration of the stability testing may depend on the type of the novel food and its proposed uses and should cover at least the end of the shelf-life. Accelerated conditions (usually at higher temperature) may be used as an alternative to stability testing under normal conditions.

If the novel food is used as an ingredient added to other foods, its stability in the processed foods should be investigated in real foods or in relevant model systems (e.g. effect of processing temperature, pH and other constituents in the processed foods).

Information on ingredients added to the novel food to improve its stability should be provided.

2.5. Specifications

The specifications define the key parameters that characterise and substantiate the identity of the novel food, as well as the limits for these parameters and for other relevant physicochemical, biochemical or microbiological parameters. The specifications will be used as key parameters, among other compositional data, to evaluate whether the data provided to demonstrate the safety are relevant to the novel food intended to be placed on the EU market. In addition, the limits set in the specifications for toxicologically and/or nutritionally relevant components will be considered in the risk assessment.

On the basis of the analytical data on the novel food provided in Sections 2.2–2.4, the applicant should propose specifications, in the form of a table, which should include the limits and information on the exact method for each of the selected parameters.

The specifications should include nutritional or biologically active components or, when these are not known, on selected chemical markers. The specifications should also include concentrations of the major groups of constituents present in the food including, for example, amino acids and proteins, lipids, carbohydrates, inorganic ions, polyphenols, alkaloids, terpenes, alkenylbenzenes, lignin, saponins, chitin, as well as the main substances within these classes.

A rationale for the selected parameters should be provided. As a minimum, the specification should include contents and/or limits for the parameters on the identity of the product; the minimal purity; and limits acceptable for impurities and degradation products, in particular those of toxicological or nutritional relevance. In the absence of legal requirements in the EU, maximum levels of contaminants (e.g. microorganisms, mycotoxins, heavy metals, pesticide residues, polycyclic aromatic hydrocarbons) should be included.

2.6. History of use of the novel food and/or of its source

2.6.1. History of the source

Data on the composition, production and on the experience from use of products from the source (other than the novel food itself) may provide relevant aspects for further consideration, for example, regarding critical substances contained in the source, potential hazards or precautions. With respect to foods derived from plants, relevant information may be found in EFSA's Compendium on Botanicals (EFSA Scientific Committee, 2012a).

2.6.2. History of use of the novel food

Data may be available on the use of the novel food as food in countries outside of the EU and on non-food uses. Such data may provide information which could be relevant for assessing the safety of the novel food.

Such information could include a description of the extent of use as a food and/or for non-food purposes, the population group for which the food has been a part of their diet, its role in the diet, the handling and preparation of the food and on precautions of use. A comprehensive literature review of human studies reporting on relevant safety outcomes should be performed. Information on the search strategy, including the sources used to retrieve pertinent data (databases, other sources), the terms and limits used (e.g. publication dates, publication types, languages, population, default tags) should be provided. Where applicable, the published literature should be reviewed by taking into account systematic review principles (EFSA, 2010). Full study reports should be provided if available.

The applicant should not only consider and limit the literature search to the novel food itself, but should also consider searching for studies with specific and safety-relevant components of the novel food and for studies with similar foods from the same or other closely related sources (e.g. other varieties or subspecies or related species of the same genus or family).

Available information on the consumption of a novel food as part of an ingredient or compound in another food should be provided in Section 2.7.4.

2.7. Proposed uses and use levels and anticipated intake

Estimated intakes of the novel food for the European population are needed to evaluate its dietary and nutritional significance and to carry out the risk characterisation. Intakes are estimated based on the proposed use levels of the novel food and data on actual food consumption.

A rationale for the target population, proposed uses and use levels, precautions and restrictions of use should be provided, with cross-referencing to relevant safety data.

Where potential health hazards have been identified on the basis of the composition, toxicological or other data, they should be discussed and adequately addressed in the proposed conditions of use to ensure that the consumption of the novel food is safe for the target population.

It is of utmost importance that the information provided in this section is precise, complete, and free of ambiguity because the safety of the novel food will be assessed under the proposed conditions of use. If information provided in this section conflicts with information relating to conditions of use in any other part of the dossier, priority will be given to the information provided in this section.

2.7.1. Target population

The applicant should unambiguously specify the intended target population, e.g. adults, the general population or certain defined population subgroups.

2.7.2. Proposed uses and use levels

The applicant should specify:

- the form of uses (e.g. as whole food, ingredient);
- the food categories[15] in which the novel food (if an ingredient) is proposed to be used;
- whether the novel food is intended to replace another food;
- the proposed maximum amounts in product(s) as consumed;
- the proposed average and maximum daily intakes for different age/gender groups as appropriate.

2.7.3. Anticipated intake of the novel food

On the basis of the information provided in Section 2.7.1 and 2.7.2, estimations of anticipated daily intakes of the novel food are required (per kg body weight and in absolute amounts). Estimations of mean and high (at least 95th percentile) anticipated daily intakes of the novel food are requested for each target population group (including, where relevant vulnerable groups such as children, pregnant and lactating women). The concurrent consumption of all food categories in which a novel food ingredient is proposed to be used should be addressed in the estimations, possibly considering different consumption scenarios. The highest estimated daily intake (i.e. at least the 95th percentile) among the population groups from a representative database (e.g. EFSA Comprehensive European Food Consumption Database or national dietary surveys) is recommended to be used as the starting point for the safety evaluation. For the intake assessment on the basis of 'per kg body weight', the EFSA guidance on default values and rounding should be taken into account (EFSA Scientific Committee, 2012b). Chronic intake estimates should be provided by default. In case the available data from toxicological or human data raise concerns regarding an acute effect, acute intake estimates should also be considered.

The application should document the methodological aspects of the intake assessment; in particular:

- the sources of data used (sources of food consumption data and food composition data);
- the scientific principles and methods applied;
- the assumptions made and their rationale; in particular with respect to the assignment of a food to a particular food category, or with respect to the model used for the calculation of high intake levels.

[15] Preferably the EFSA Food classification system should be used (EFSA, 2011b).

The Panel proposes a tiered approach where the first step makes use of the summary statistics of the EFSA Comprehensive Food consumption Database.[16]

Summary statistics of food consumption are available on the EFSA website in the form of spreadsheets. Detailed information on the database and guidance on its use have been published by EFSA (EFSA, 2011a). Anticipated daily intakes for mean and high-percentile consumers can be calculated through the combination of the intended use level in each food category with mean and high chronic consumption values from the database, respectively.

The use of the EFSA Food Additive Intake Model (FAIM) tool[17] (which is also based on summary statistics of the EFSA Comprehensive Food Consumption Database) may serve as an appropriate alternative in tier 1. The FAIM tool was developed to support the calculation of chronic exposure to food additives in the regulatory framework of food additives Regulation (EU) 1333/2008. Exposure assessment of food additives and intake assessment of novel food ingredients share common principles. Thus, the FAIM tool may be used by applicants for the intake assessment of novel foods used as ingredients where the food categories to which the ingredient is intended to be added, match reasonably with the food categories covered in the FAIM tool. It allows the applicant to estimate the mean and high-level exposure to food ingredients for different population groups throughout several European countries by means of pre-defined exposure calculation worksheets. For the calculation of high percentiles of daily intake, the model assumes that an individual might be a high-level consumer of one food category only and would be an average consumer of all the remaining food groups. Thus, the FAIM tool adds the highest of the high-levels of intake from one food category (calculated for consumers only) to the mean intake values for the remaining categories (calculated for the total population).

Summary statistics from the EFSA Comprehensive European Food Consumption Database (incl. FAIM tool) provide valuable screening estimates of intake. In some cases, such estimates may bring sufficient information, if high intake estimates are below health-based guidance values (e.g. acceptable or tolerable daily intake). In other cases, where more refined estimates are needed, the applicant should consider more detailed assessments, such as intake calculations based on individual data from national food consumption surveys (tier 2).

The applicant should consider and discuss the uncertainties related to the assessment; in particular, sources of under- or over-estimations. To this end, the guidance from the EFSA Scientific Committee related to uncertainties in dietary exposure assessment should be considered (EFSA, 2006).

Where a novel food is intended to replace another food already existing on the market, the applicant should provide their considerations and explanations why it is reasonable to expect that the novel food would replace that food. In such cases, estimates of the consumption of the food that is intended to be replaced could be used for estimating consumption of the novel food.

2.7.4. Combined intake from the novel food and other sources

Other potential sources of intake of the novel food should be taken into account (such as natural occurrence in food). In such cases, an estimation of the mean and high daily intake of the constituent from other sources should be considered, in order to assess the extent of the additional intake of the constituent resulting from its intended use as a novel food, in relation to existing dietary intake.

Information should be provided on:

- mean and high daily intakes[18] of the novel food from its proposed uses and maximum use levels;
- mean and high daily intakes from natural sources (i.e. from the background diet);
- daily intake from food fortification and supplements;
- daily intake from other uses.

For estimating total daily intake of the constituent, mean and high anticipated intakes from its intended use as a novel food and current intake from background diet should be considered and conservative scenarios should be applied.

[16] http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

[17] https://www.efsa.europa.eu/sites/default/files/assets/faimtemplateinstructions.pdf and https://www.efsa.europa.eu/sites/default/files/assets/faimtemplate.xls

[18] 'High daily intakes' usually expressed by the 95th or 97.5th percentile.

Any other potential non-dietary sources (e.g. from consumer products such as cosmetics, and from pharmaceuticals) should also be considered and taken into consideration in the total exposure assessment, where relevant.

2.7.5. Estimate of exposure to undesirable substances

Exposure estimates are also to be provided for relevant undesirable substances identified in the compositional analysis, for example, potential secondary plant metabolites, residues, contaminants or degradation products. These may be present in the novel food due to its source or the manufacturing process, as well as due to its use and storage.

The same approach as that used for the intake estimate of the novel food should be followed, in order to describe the anticipated exposure for average and high consumers to these constituents for the relevant population groups.

2.7.6. Precautions and restrictions of use

When proposing precautions (including directions for its preparation and/or use) and restrictions of use, all available information on safety should be taken into consideration.

The applicant should specify the population (sub)groups (including population groups with certain physiological conditions) which should avoid consumption of the novel food and include the rationale.

2.8. Absorption, distribution, metabolism and excretion (ADME)

Data on absorption, distribution, metabolism and excretion (ADME) in humans and animals are important for the assessment of both the nutritional and toxicological impact of a novel food.

Applicants are advised to consult the data requirements and tiered approach to kinetic testing which are described in Section 4.1 on 'Toxicokinetics (ADME)' of the EFSA guidance for food additive evaluations (EFSA ANS Panel, 2012). The Panel considers that the kinetics of single substances and simple mixtures should normally be tested according to the same principles as those applied to food additives. As a default, absorption of the novel food or its breakdown products should be assessed (tier 1). Demonstration of negligible absorption may provide a scientific justification for not undertaking higher tiered toxicological studies.

For food additives in the form of complex mixtures, the ANS guidance states that

> 'conventional metabolism and toxicokinetic studies may not be feasible for all components in the mixture, but should be provided for toxicologically relevant constituents. Toxicologically relevant constituents are generally considered to be the major components and those other components with known or demonstrable biological or toxicological activity, and should be determined on a case-by-case basis with a scientific justification and the rationale for their selection provided'.

Whole foods should be tested like complex mixtures. The design of kinetic studies may be modified based on the particular complex mixture/whole food being tested.

For novel foods, ADME assessment should also address nutritionally significant constituents where kinetic data on these constituents are important considerations for the evaluation of the nutritional impact of the novel food (Section 2.9).

With respect to novel foods consisting of 'engineered nanomaterials', applicants should consider the specific requirements and follow the approach as set out in the EFSA Scientific Committee guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain (in particular, sections on *in vitro* digestion studies and ADME studies) (EFSA Scientific Committee, 2011a). The Panel notes that this EFSA guidance is currently being updated by EFSA (EFSA-Q-2016-00281[12]).

2.9. Nutritional information

The applicant should demonstrate that the novel food is not nutritionally disadvantageous for consumers under the proposed conditions of use. For this purpose, in the context of this guidance, the term nutritional information specifically refers to the role that the novel food may play in the diet in terms of its contribution to or interaction with nutrient intakes.

Nutritional information on the novel food should include details of its nutrient composition and address bioavailability taking into account influences of the production process, storage and further processing that may be required prior consumption. In some cases, i.e. where cooking is necessary for the intended use, e.g. to reduce or inactivate antinutritional substance, such effects should be

discussed by the applicant. The content and effect of antinutritional factors in the novel food (e.g. inhibiting absorption or modifying bioavailability) and other known and suspected interactions with nutrients should also be assessed.

Levels of use and estimated intakes for the target population should be taken into account as specified in Section 2.7 ('Proposed uses and use levels and anticipated intake of the novel food'). Intakes of relevant substances from the background diet, both nutritional and antinutritional, should be considered for establishing mean and high daily intake scenarios. The resulting estimates should be discussed in the context of available dietary reference values including tolerable upper intake levels ('upper levels'). Intake estimates for potentially antinutritional substances should be compared with health-based guidance (e.g. ADI) values, if available. Vulnerable subgroups such as young children, pregnant and lactating women or subjects with particular metabolic or physiological characteristics should be specifically considered on a case-by-case basis. Where a novel food is intended to replace another food, or when a novel production process is applied to a food which is a relevant source for nutrients, the applicant should demonstrate that the novel food does not differ in a way that it would be nutritionally disadvantageous for the consumer under the proposed conditions of use.

Apart from an evaluation of the compositional data and an appraisal of the relevant literature and databases, in specific cases, data from investigations in *in vitro* and/or in animal models and/or human studies may be needed to address the interaction of the novel food with the diet and nutrients. The necessity for such studies may arise from information on the source, the composition and the production of the novel food, from documented experience on the uses, preparation and/or handling of the novel food (e.g. foods which have been consumed in third countries), outcomes from studies on ADME, and from pharmacological, mechanistic, feeding, toxicological and human studies.

2.10. Toxicological information

2.10.1. General considerations

Toxicological studies should be carried out with the novel food as intended to be marketed, i.e. the test material should be manufactured according to the production process described in Section 2.3, meet the compositional characteristics provided in Section 2.4 and meet the specifications proposed in Section 2.5. If this is not the case, a rationale should be provided to substantiate why the test material used for the toxicological studies is appropriate for the safety assessment of the novel food.

Toxicological studies should be conducted in accordance with international guidelines (e.g. OECD) and according to the principles of GLP.

The Panel notes that all relevant knowledge on the novel food should be considered in order to make decisions on whether and which toxicity studies are necessary. Important elements include:

- the identity, chemical structure, composition and physico-chemical properties of the novel food (Sections 2.1–2.5);
- available information on previous human consumption of the novel food and its source (Section 2.6);
- anticipated use(s), maximum use levels and the resulting intakes (Section 2.7);
- available kinetic data (Section 2.8);
- available toxicological data on the novel food or its constituents;
- available human studies;
- available relevant information on non-food uses (e.g. cosmetics, chemicals, pharmaceuticals);
- in case of insufficient experimental data also: (quantitative) structure–activity relationship ((Q)SAR) data.

Toxicological data on structurally related substances ('read-across') should be considered. The Panel considers that the tiered toxicity testing approach proposed for food additives should be considered as the default approach. It integrates the core areas of kinetics, genotoxicity, repeated dose toxicity testing (subchronic, chronic toxicity and carcinogenicity) and reproductive and developmental toxicity (EFSA ANS Panel, 2012). Additional studies may be needed to examine specific biological processes which may not be fully considered in the core areas for evaluation. Other studies that may be relevant include, e.g. immunotoxicity, hypersensitivity and food intolerance, studies on neurotoxicity, endocrine activity and mode of action.

Deviations from this approach and/or its non-applicability should be reasoned with sound scientific arguments based on the elements listed in the bullet points above.

The types and purposes of toxicity studies are outlined in Sections 2.10.2–2.10.6 of the present guidance for novel food applications. Specific cases are described in Section 2.10.7.

The Panel notes that the Threshold of Toxicological Concern (TTC) approach might be helpful when assessing the risk of low exposure to substances such as impurities, metabolites and degradation products present in (or derived from) the novel food for which toxicity data may not be available. The applicant is advised to consult the EFSA guidance on the concept of TTC (EFSA Scientific Committee, 2012c).

2.10.2. Genotoxicity

The assessment of genotoxic potential is a basic component of chemical risk assessment (EFSA Scientific Committee, 2011b). Genotoxicity testing of novel foods should aim at identifying substances which could cause heritable damage in humans, and at predicting potential genotoxic carcinogens in cases where carcinogenicity data are not available.

The Scientific Committee recommended a step-wise (tiered) approach for the generation and evaluation of data on genotoxic potential (EFSA Scientific Committee, 2011b). A basic battery of *in vitro* tests is recommended as a first step, and follow-up approaches in the event of positive results from the basic battery are provided. Recommendations on test types, results interpretations and other issues in testing the genotoxicity of substances present in food are described in detail in the Opinion of the Scientific Committee.

The Panel notes that the approach proposed by the Scientific Committee in principle applies to novel foods. For some complex mixtures and whole foods, it may be necessary to focus on specific constituents of the novel food. Deviations can be argued on a case-by-case basis.

2.10.3. Subchronic toxicity

In line with the guidance for food additives, a subchronic toxicity study should normally be submitted (EFSA ANS Panel, 2012). The major objective of such study is to identify any adverse effects following prolonged exposure via an appropriate oral route.

It should also allow determination of the relevant BMDL (EFSA Scientific Committee, 2009b) or the NOAEL. The subchronic toxicity study can provide indications on the need for additional studies on specific effects (Sections 2.10.4–2.10.6).

The study should normally be conducted for a period of at least 90 days (OECD TG 408), modified to include assessment of some additional parameters described in the more recent guideline on repeated-dose 28-day oral toxicity studies in rodents (OECD TG 407). The additional parameters place more emphasis on endocrine-related endpoints. The modified 90-day study should allow for the identification of substances with the potential to cause neurotoxic, immunological, reproductive organ effects or endocrine-mediated effects. When kinetics testing indicates a lack of systemic availability, studies should at least investigate both pathological and physiological effects in the gastrointestinal tract. The effects of unabsorbed materials on gastrointestinal function and tolerance also need to be investigated. Specific to novel foods, the Panel notes that additional markers of potentially adverse nutritional and/or metabolic effects should be considered on a case-by-case basis, according to the available body of evidence and the nature of the novel food.

For 'whole foods', the testing requirements should be determined using a case-by-case approach, as special considerations are required with regard to dose selection and the avoidance of possible nutritional imbalances. For further guidance on the conduction of subchronic oral toxicity studies with 'whole foods', the applicant is advised to consult the relevant guidance from the Scientific Committee (EFSA Scientific Committee, 2011c).

2.10.4. Chronic toxicity and carcinogenicity

Important considerations which can trigger the need for chronic toxicity or carcinogenicity studies include, among others, critical findings in the subchronic study as well as results of *in vitro* or *in vivo* toxicity tests, including genotoxicity tests. Further guidance on the triggers for these studies and their implementation are outlined in the guidance on food additives (EFSA ANS Panel, 2012) and respective OECD Guidelines (OECD TG 451, 452 or 453).

2.10.5. Reproductive and developmental toxicity

Decisions on whether tests for reproductive and developmental toxicity are necessary need to be considered in the light of kinetic and toxicity data, including read-across data.

Any indications of effects on reproductive organs or parameters, for example in the modified 90-day oral toxicity, will trigger testing for reproductive and developmental toxicity. Reproductive and developmental toxicity testing may not be required, if argued on a case-by-case basis.

2.10.6. Human data

Human studies, if available, should be provided if they contain information relevant for the safety assessment, such as physical examination, blood chemistry, haematology, urine analysis, blood pressure and organ function tests and/or monitoring of adverse reactions. Relevant data may be derived from the use of the novel food for medical purposes or from epidemiological studies. Additional human studies may be needed to investigate further potentially adverse effects, e.g. to address adverse effects observed in toxicological studies. In those cases where the novel food may exert pharmacodynamic effects, specific studies may be required to demonstrate that the proposed consumption and use of the novel food do not raise safety concerns.

The data from intervention studies and observational studies in humans should be organised according to a hierarchy of study designs and research questions, reflecting the relative strength of evidence which may be obtained from different types of studies. Studies with the highest level of scientific evidence should be presented first.

2.10.7. Specific cases

2.10.7.1. Insects

The EFSA Scientific Committee has identified potential hazards related to the use of farmed insects as food (EFSA Scientific Committee, 2015). These should be considered in applications for novel foods which consist of, are isolated from, or are produced from farmed insects, taking into account the species and substrate to be used, as well as methods for farming and processing. Insects collected from the wild may bear additional biological and chemical hazards which should be considered and addressed.

2.10.7.2. Microorganisms

A wide variety of microorganisms and fungal species are used in food and feed production, either directly (e.g. to produce fermented foods) or as sources of additives, food enzymes or other components of foods. Many of them are present in high concentrations as viable microorganisms in the final product. Some of these microorganisms have a history of safe use and have been assigned the qualified presumption of safety (QPS) status by EFSA which constitutes a preliminary safety assessment (EFSA BIOHAZ Panel, 2015). This QPS list includes taxonomic groups that have not raised safety concerns so far, and others for which some safety concerns exist but could be defined and addressed with 'qualification' as expressed in the QPS list. Therefore, any strain of microorganism, the identity of which could be unambiguously established and assigned to a QPS group, would be freed from the need for an exhaustive safety assessment apart from satisfying the criteria and qualifications specified previously (EFSA, 2008) and assessing the risk of antimicrobial resistance (EFSA FEEDAP Panel, 2012).

For those microorganisms for which safety properties are less well understood, a safety assessment should be provided. The safety assessment of microorganisms is primarily based on unambiguous taxonomic classification at species level and complete strain characterisation by fully assembled and validated whole-genome sequence analysis to enable the detection of virulence-related genes, antibiotic resistances and their potential horizontal transfer, and other potentially adverse metabolic features (e.g. toxins, D-lactate, etc.). Phenotypic characterisation of the potential antimicrobial resistances (intrinsic or acquired) should also be carried out following EFSA recommendations applying to all microorganisms used in food or feed production (EFSA FEEDAP Panel, 2012). When appropriate, depending on the taxonomic classification and genome information of the microorganism, other potentially adverse phenotypic features should be assessed (e.g. potential toxin production, haemolytic activity, infectivity, adverse immune effects, etc.). For safety assessment, information should be provided on the numbers of viable microorganisms in the final product and stability.

2.10.7.3. Engineered nanomaterials

If the novel food is containing or consisting of 'engineered nanomaterials', the applicant should consider the guidance on the risk assessment of the application of nanoscience and nanotechnologies

in the food and feed chain from EFSA's Scientific Committee (EFSA Scientific Committee, 2011a) which is currently under review by EFSA (EFSA-Q-2016-00281[19]).

2.11. Allergenicity

Food allergens are mostly proteins. Hence, the allergenic potential of a novel food containing no protein (or peptides) is very low. An accurate description of the methods used for the analysis of the protein content in the novel food (including the limits of detection and quantification) and the results from those analyses should be provided in Section 2.4.

The default assumption for novel foods containing proteins is that they have allergenic potential. The allergenic potential of the novel food should be explored by considering its composition, particularly its protein(s), its source (including taxonomic relationships), the production process, and available experimental and human data, including information on cross-reactivity. This comprises a comprehensive literature review in order to retrieve available information on sensitisation, case reports of allergic reactions, and/or allergenicity studies (*in vitro*, in animals, in humans) of the novel food and/or its source(s).

Information on appropriate methods to further investigate the potential allergenicity of foods is provided in the Scientific Opinion of the NDA Panel on the evaluation of allergenic foods and food ingredients for labelling purposes (EFSA NDA Panel, 2014). Such methods include:

2.11.1. Protein analysis

- Protein content in the novel food,
- Molecular weight of the potentially allergenic protein, heat stability, sensitivity to pH, digestibility by gastrointestinal proteases,
- Degree of sequence homology with known allergens,
- Immunological tests (e.g. western blotting).

2.11.2. Human testing

- Detection of specific IgE antibodies,
- Skin prick testing,
- Double-blind placebo-controlled food challenge studies.

If an applicant wishes to demonstrate that the novel food is unlikely to trigger adverse reactions in sensitive individuals under the proposed conditions of use, the approach outlined in the EFSA guidance on the preparation and presentation of applications pursuant to Article 6 Paragraph 11 of Directive 2000/13/EC, as amended (EFSA NDA Panel, 2013) should be followed.

Applicants for novel foods which potentially contain allergens listed in Annex II of Regulation (EU) No 1169/2011 and who seek exemption from mandatory labelling are advised to file an application pursuant to Article 21 paragraph 2 of Regulation 1169/2011 (previously Article 6 Paragraph 11 of Directive 2000/13/EC) by using the afore-mentioned guidance document (EFSA NDA Panel, 2013).

2.12. Concluding remarks

The applicant should integrate the data presented in the previous sections to provide their overall considerations on how the information supports the safety of the novel food under the proposed conditions of use.

Where potential health hazards have been identified (e.g. on the basis of the composition of the novel food, its production process, its history of use, the results from animal and/or human studies), they should be discussed in relation to the anticipated intakes of the novel food and the proposed target populations.

In particular, the applicant should address:

- the relevance of toxicologically relevant components (e.g. impurities, by-products, residues, chemical or microbiological contaminants) in relation to their estimated intakes, possible background exposure and their health-based guidance values (e.g. tolerable daily intakes), when applicable;
- the results of toxicity studies;

[19] http://registerofquestions.efsa.europa.eu/roqFrontend/ListOfQuestionsNoLogin?0&panel=SCER

- any adverse effects identified through the human data;
- sources of uncertainties.

3. Part 3: Annexes to the dossier

- The glossary or abbreviations of terms quoted throughout the dossier,
- The certificates (on the accreditation of laboratories, certificates of analyses),
- Full copies/reprints of all pertinent scientific data (published and unpublished),
- Full study reports,
- Scientific opinions of national/international regulatory bodies.

References

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Abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
BMDL	lower confidence limit for a benchmark dose
CAS	Chemical Abstracts Service
EMA	European Medicines Agency
FAIM	Food Additive Intake Model
GC–MS	gas chromatography–mass spectrometry
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMM	genetically modified microorganism
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis Critical Control Point
ICH	International Conference on Harmonisation
IR	infrared spectroscopy
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
LC–MS	liquid chromatography–mass spectrometry
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NMR	nuclear magnetic resonance
NOAEL	no adverse effect level
OECD	Organisation for Economic Co-operation and Development
PCBs	polychlorinated biphenyls
QPS	qualified presumption of safety
(Q)SAR	(quantitative) structure activity relationship
TTC	threshold of toxicological concern
UV-VIS	ultraviolet-visible spectroscopy